REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 1-64 were previously canceled without disclaimer or prejudice thereof, and claims 66, 68, 70 and 72 are requested to be canceled in this paper without disclaimer or prejudice thereof.

Claims 65, 67, 69 and 71 are currently being amended. Claims 65 and 69 are amended to recite "serum or plasma" samples instead of "a sample," to include a "contacting" step in the diagnostic method as suggested by the Examiner, and to omit reference to polypeptide or nucleic acid sequence variants. Claim 65 has also been amended to recite "[a] method for diagnosing a pregnant woman at increased risk of preeclampsia..." instead of "[a] method for diagnosis of preeclampsia...." Exemplary support for serum or plasma samples is found in cancelled claims 66 and 70. Exemplary support for the "contacting" step is found at page 16, lines 1-3 of the specification. Exemplary support for diagnosing pregnant woman at increased risk of preeclampsia can be found in the specification at page 10, lines 10-12.

Claims 67 and 71 are amended to omit reference to measurement of "expression of any of the genes..." and instead relate to measurement of protein expression as suggested in the Office Action.

The amendments add no new matter and entry and examination thereof is respectfully requested. After amending the claims as set forth above, claims 65, 67, 69 and 71 are now pending in this application.

II. Claim rejection – 35 U.S.C. § 112, second paragraph

A. Claims 65-72

Claims 65-72 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically the Office Action asserts that claims 65 and 69 omit essential steps and "minimally [should] include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for determination." The Office Action alleges that "no contacting step can be found in the claims." (Office Action at page 2). Applicants respectfully traverse the rejection.

Claims 66, 68 and 70 are canceled, thereby obviating the rejection with respect to these claims.

Without conceding to the correctness of the Office Action assertion and solely to expedite prosecution, independent claims 65 and 69 have been amended to recite "contacting the sample with reagents necessary for determining the amount of a marker in the sample..." as suggested by the Examiner.

Accordingly, the reasons for rejection are obviated, and reconsideration and withdrawal of the rejection is respectfully requested.

B. Claims 65 and 69

Claims 65b(ii) and 69b(ii) are rejected because the phrase "any of the amino acid sequences according to i) of at least 95% over 100 amino acid residues" allegedly lacks sufficient antecedent basis. Applicants respectfully traverse this rejection.

Again, without conceding to the correctness of the Office Action assertion and solely to expedite prosecution, claims 65 and 69 have been amended to omit this phrase.

Thus, the reasons for rejection are obviated, and reconsideration and withdrawal of the rejection is respectfully requested.

III. Claim rejection – 35 U.S.C. § 112, first paragraph, enablement

Claims 65-72 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. The Office Action admits that the specification is enabling for "a method for the diagnosis of preeclampsia comprising (a) obtaining a serum or plasma sample from a pregnant woman in the late 2nd and early 3rd trimester, (b) contacting samples from the pregnant woman with anti-ADAM 12-S (SEQ ID NO: 4) antibodies and (c) comparing the level of ADAM 12-S in said serum sample to a gestational age matched serum obtained from a healthy woman, wherein an increase in ADAM 12-S level in the serum is indicative of preeclampsia." (Office Action at page 3). The Office Action continues, however, asserting that the claimed methods are *not enabled* for (1) diagnosis using "any sample"; (2) diagnosis via detection of ADAM-12S variants; (3) diagnosis of eclampsia, pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation; (4) diagnosis by detecting ADAM 12S in the second trimester because ADAM 12S is also a marker for Down Syndrome; (5) diagnosis via detecting gene expression of additional genes (*e.g.*, those genes recited in claims 67 and 71) in serum or plasma samples; (6) determining the amount of the marker (*e.g.*, ADAM-12S) in a sample by methods other than antibodies. Applicants respectfully traverse these grounds for rejection.

Claims 66, 68 and 70 have been cancelled, thereby obviating the rejection with respect to these claims.

The rejections as they relate to claims 65, 67, 69 and 71 are addressed below.

A. The use of "any sample" and detection of ADAM 12S variants

The Office Action asserts that the claimed diagnostic methods are not enabled if "any sample" from the patient is used, or if the claimed ADAM-12S variants are detected. (Office Action at pages 3-4). Applicants respectfully traverse the rejection.

Without conceding to the correctness of the Office Action assertion and solely to advance prosecution, independent claims 65 and 69 have been amended to specify "serum or plasma samples" and to omit reference to the detection of sequence variants.

Accordingly, the grounds for rejection summarized as points (1) and (2) above are obviated, and reconsideration and withdrawal of this aspect of the rejection is respectfully requested.

B. Diagnosis of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation

The Office Action asserts that the specification is not enabling for the diagnosis of pregnancy induced hypertension, HELLP syndrome and intrauterine growth retardation because it is unclear whether these conditions are caused by or result from preeclampsia. (*See e.g.*, Office Action at pages 3-4). Applicants respectfully traverse the rejection.

Without conceding to the correctness of the Office Action assertion, and solely to expedite prosecution, independent claim 69 has been amended to omit reference to pregnancy induced hypertension and intrauterine growth retardation. However, HELLP syndrome is a well recognized complication of preeclampsia (*see e.g.*, Barton, *et al.*, *Gastrointestinal complications of pre-eclampsia*, Seminars in Perinatology, 179-188 (2009), abstract and page 179 bridging first and second column, Exhibit A; Hofmeyr, *et al.*, *Proteinuria as a predictor of complications of pre-eclampsia*, BMC Medicine, 7(11):1-7, (2009), paragraph bridging pages 1 and 2, Exhibit B). Since HELLP syndrome is a complication of preeclampsia, a test that diagnoses the risk of preeclampsia also diagnoses the risk of this complication.

Accordingly, the grounds for the rejection summarized as point (3) above are either obviated or improper, and reconsideration and withdrawal of this aspect of the rejection is respectfully requested.

C. ADAM 12S is a marker for Down Syndrome in the second trimester

The Office Action asserts that because increased expression of ADAM-12S is also a marker for Down syndrome in the second trimester, it would not be clear "whether an increase in ADAM 12-s in the second trimester would indicate preeclampsia or Down syndrome" (Office Action at page 4).

Applicants fail to understand why this is a hindrance to the enablement of the present methods. After reading the specification, a skilled artisan would understand that a patient exhibiting elevated ADAM-12S levels in the second or third trimester of pregnancy is a candidate for developing preeclampsia and should be closely monitored for any signs or symptoms of the disease.

It is generally established in medicine that very few diagnostic assays or procedures, on their own, allow for diagnosing the presence or absence of a disease without any additional tests. Typically, a medical diagnosis is a differential diagnosis. The presence of a specific sign, symptom or positive test result can in most cases be attributed to the presence of more than one disease. Consequently, further tests are performed to rule out possible diseases explaining the sign, symptom or positive test result until only one disease remains which explains all signs, symptoms and test results. In the present case, an increase of ADAM-12S protein in serum or plasma during the second trimester indicates preeclampsia and/or Down syndrome. Other diagnostic procedures would be performed to rule out either the presence/risk of preeclampsia or the presence of Down syndrome in the fetus. As recited in claim 65(e), "a higher determined amount of the marker as compared to the reference amount of the marker *is indicative* of preeclampsia"; the claims does not recite that a higher determined amount of the marker is compared to the reference amount of the marker is *conclusive* of preeclampsia. Thus, while

further tests would be performed to determine whether the fetus has Down syndrome, it is also likely that the mother would be rigorously monitored for signs and symptoms of preeclampsia for the duration of the pregnancy, regardless of fetal status. The ability to detect an increased risk (*e.g.*, an indication) of preeclampsia before the actual onset is a significant diagnostic advantage.

Accordingly, the grounds for this rejection summarized as point (4) are either obviated or improper, and reconsideration and withdrawal of this aspect of the rejection is respectfully requested.

D. Detection of the expression of additional genes

The Office Action asserts that the specification does not enable the determination of "gene expression" of the genes listed in claims 67 and 71 in serum or plasma. Specifically, the Office Action asserts that "it is not clear how *gene expression* can be measured in a serum sample or a plasma sample." (Office Action at page 5, emphasis added). Applicants respectfully traverse this ground for rejection.

Without conceding to the correctness of the Office Action assertion and solely to expedite prosecution, claims 67 and 71 have been amended to omit reference to measurement of gene expression and to instead recite "a diagnostic agent for the measurement of expression of any of the *proteins* selected from the group consisting of...." The skilled artisan would clearly understand how to detect proteins in serum or plasma using well-known methods (*e.g.*, antibodies, aptamers, natural or artificial substrates, etc.).

Accordingly, the reasons for rejection summarized as point (5) are obviated, and reconsideration and withdrawal of this ground for rejection is respectfully requested.

E. Determining the amount of the marker (*e.g.*, ADAM-12S) in a sample by methods other than antibodies

The Office Action asserts that "beside using the anti-ADAM 12s antibodies, the specification fails to provide guidance on how to determine the amount of a marker in the sample." (Office Action at page 5). Applicants respectfully traverse this ground for rejection.

The specification teaches that ADAM-12 protein can be measured by well known methods, for example by cellular responses, the amount of bound ligands, labels or enzymatic reaction products (*see e.g.*, specification at page 15, lines 25-27). The present specification also teaches that HB-EGF, P-LAP, IGFBP-3 and IGFBP-5 are ligands of ADAM-12 and that ADAM-12S cleaves HB-EGF, P-LAP, IGFBP-3 and IGFBP-5 (*see e.g.*, specification at page 14, lines 27-31; page 19, lines 19-20). Accordingly, ADAM-12S can be detected by an activity assay in which one or more of the disclosed substrates (HB-EGF, P-LAP, IGFBP-3 and IGFBP-5) is contacted with a sample. If the substrate is cleaved, ADAM-12S is present. In addition, the amount of cleaved product formed over a fixed period of time will allow the skilled artisan to determine if there is more ADAM-12S in a sample as compared to a control. Alternatively, ADAM-12S can be detected by a ligand binding assays. For example, HB-EGF, P-LAP, IGFBP-3 and/or IGFBP-5 can be labeled, and the amount of the ligand-ADAM-12S complex can be measured by methods well known in the art.

Given that 1) methods to detect and quantify enzymatic reaction products or ligand-bound complexes are well known in the art, and 2) that the enzyme and substrate/ligand are detailed in the specification, it is asserted that the specification provides more than sufficient information for the skilled artisan to "determine the amount of marker in the sample" by methods other than antibody detection.

Accordingly, the reasons for rejection summarized as point (6) are improper and reconsideration and withdrawal of this ground for rejection is respectfully requested.

F. Summary

For at least the reasons described above, the pending claims are fully enabled by the specification, and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

IV. Claim rejection – 35 U.S.C. § 112, first paragraph, written description

Claims 65-72 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the written description requirement. Specifically, the Office Action asserts that the specification fails to describe "a protein having an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences [presented in SEQ ID NO: 4] (according to i) of at least 95% over 100 amino acid residues." (Office Action at page 6). Applicants respectfully traverse this ground for rejection.

Without conceding to the correctness of the Office Action assertion and solely to expedite prosecution, the claims have been amended to omit reference to the detection of polypeptide variants.

Accordingly, the reason for rejection is obviated, and reconsideration and withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

V. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to

Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: December 16, 2009

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EXHIBIT A

ELSEVIER

SEMINARS IN PERINATOLOGY

Gastrointestinal Complications of Pre-eclampsia

John R. Barton, MD,* and Baha M. Sibai, MD†

Gastrointestinal complications of pre-eclampsia can occur and have the risk of being life-threatening for the mother and fetus. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome has been recognized as a complication of pre-eclampsia for decades. Pregnancies complicated by this syndrome require a well-formulated management plan, including assessing and stabilizing the maternal condition as well as evaluating fetal well-being. Patients with HELLP syndrome should receive anti-seizure prophylaxis with magnesium sulfate, treatment for severe hypertension, and correction of coagulopathy, if present. The potential benefits of expectant management of HELLP syndrome in those remote from term and the use of corticosteroids to improve maternal outcome remain experimental. Computed tomography or ultrasound of the abdomen should be performed if a subcapsular hematoma of the liver is suspected. If a ruptured hematoma is confirmed, massive transfusions and laparotomy are indicated. Ischemia associated with pre-eclampsia cannot only damage the liver but also the pancreas and gallbladder.
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KEYWORDS severe pre-eclampsia, HELLP syndrome, hepatic hepatoma, hepatic rupture

Pre-eclampsia is a form of hypertension that is unique to human pregnancy. Although the exact etiology of pre-eclampsia remains unknown, vascular endothelial injury is a frequent ultrastructural finding.[1] The extent and location of the endothelial injury can define the maternal severity and presentation of pre-eclampsia. While renal and neurologic manifestations of pre-eclampsia are more common, gastrointestinal complications of pre-eclampsia can occur and have the risk of being life-threatening. A misdiagnosis can lead to delay in hospitalization, stabilization, and delivery. This review discusses the diagnosis and management of gastrointestinal complications of pregnancy with an emphasis on hepatic manifestations.

Hepatic Involvement of Pre-Eclampsia

Abnormal liver function tests and hemolysis have been recognized as complications of pre-eclampsia-eclampsia for many years.[2,3] In 1982, Weinstein described 29 cases of severe pre-eclampsia-eclampsia complicated by thrombocytopenia, abnormal peripheral smear, and abnormal liver function tests.[4] He suggested that this collection of signs and symptoms constituted an entity separate from severe pre-eclampsia and coined the term *HELLP syndrome*: *H* for hemolysis, *EL* for elevated liver enzymes, and *LP* for low platelets. Since then, numerous articles and case reports describing this syndrome have appeared in the medical literature. In addition, the presence of this syndrome has become a major cause of litigation against obstetricians, involving cases of alleged misdiagnosed pre-eclampsia, particularly in those patients complicated by severe liver involvement of their disease.

The diagnostic criteria used for HELLP syndrome are variable and inconsistent. Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is the hallmark of the triad of HELLP syndrome.[5,6] The classical findings of microangiopathic hemolysis include abnormal peripheral smear (schistocytes, burr cells, echinocytes), elevated serum bilirubin (indirect form), low serum haptoglobin levels, elevated lactate dehydrogenase (LDH) levels, and significant drop in hemoglobin levels.

There is no consensus in the literature regarding the liver function test to be used or the degree of elevation in these tests to diagnose elevated liver enzymes.[3,6] In the original report by Weinstein, he mentioned abnormal serum levels of aspartate transaminase (AST), abnormal alanine transferase, and abnormal bilirubin values; however, levels were not stated.[4] In addition, he made no mention of LDH as a diagnostic test of liver involvement. In subsequent studies where elevated liver enzymes were mentioned (either AST or abnormal alanine transferase), the values considered abnor-

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mal ranged from 17 to 72 U/L.[5] In clinical practice, many of these values are considered normal or slightly elevated.

Low platelet count is the third abnormality required to establish the diagnosis of HELLP syndrome. There is no consensus among various published reports regarding the diagnosis of thrombocytopenia. The reported cut-off values have ranged from 75,000 to 279,000/mm^3.[7-11] Martin and coworkers,[12] in a retrospective review of 302 cases of HELLP syndrome at the University of Mississippi, Jackson, devised the following classification of subpopulations based on platelet count nadir. They defined class 1 HELLP syndrome as a platelet nadir below 50,000/mm^3, whereas those with platelet nadirs between 51,000 and 100,000/mm^3 were defined as class 2. Finally, class 3 represents a platelet nadir between 101,000 and 150,000/mm^3. These classes have been used to predict the rapidity of postpartum disease recovery,[12] risk of recurrence of HELLP syndrome,[13] perinatal outcome, and the need for plasmapheresis.[14] Miles and associates,[15] from the same institution, reported a strong association between the presence of HELLP syndrome and eclampsia. In this study, the HELLP syndrome was present in 30% of patients with postpartum eclampsia and in 28% of patients having eclampsia before delivery. As a result, they suggested that the presence of HELLP syndrome may be a predisposing factor in the development of eclampsia.[15] The criteria for the diagnosis of the HELLP syndrome by several authors include the laboratory findings summarized in Table 1.

An essential step in management is to confirm or exclude the diagnosis of HELLP syndrome from other conditions listed in Table 2. Laboratory evaluation should include a complete blood count with platelet count, a peripheral smear, coagulation studies, serum AST, creatinine, glucose, bilirubin, and LDH levels. Our diagnosis of HELLP syndrome requires the presence of all the following: platelet count less than 100,000/mm^3, an AST ≥70 IU/L (>2 × upper limit for our normal values), abnormal peripheral smear, an LDH ≥600 IU/L (>2 × upper limit of normal), and/or bilirubin ≥1.2 mg/dL. Those who do not have all these parameters are considered to have partial HELLP syndrome.

Clinical Presentation of HELLP Syndrome

In the series reported by Sibai and associates,[16] patients with HELLP syndrome were significantly older (mean age, 25 years) than patients with severe pre-eclampsia-eclampsia without features of HELLP syndrome (mean age, 19 years). The incidence of the syndrome was significantly higher in the white population and among multiparous patients. The incidence of HELLP syndrome is also higher in pre-eclamptic patients with conservative management of their disease. Coincidentally, medial complications (notably diabetes mellitus and lupus nephritis) were no more common among the patients with HELLP syndrome. Other authors have made similar observations.[11,17]

Table 1 Laboratory Criteria for HELLP Syndrome

	Platelet Count	AST	LDH
Sibai et al.[16]	<100,000/mm^3	≥70 U/L	≥600 U/L
Martin et al.[63]	<150,000/mm^3	≥40 U/L	≥600 U/L
van Pampus et al.[25]	<100,000/mm^3	>50 U/L	>600 U/L
Visser and Wallenburg[24]	<100,000/mm^3	>30 U/L	a

Abbreviations: a, not included in the author's criteria; AST, serum levels of aspartate transaminase; LDH, serum levels of lactate dehydrogenase.

Table 2 Medical and Surgical Disorders Confused with the HELLP Syndrome

- Acute fatty liver of pregnancy (AFLP)
- Appendicitis
- Catastrophic antiphospholipid syndrome
- Cholecystitis
- Gastroenteritis
- Glomerulonephritis
- Hemolytic uremic syndrome (HUS)
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Intracranial hemorrhage
- Nephrolithiasis
- Pancreatitis
- Peptic ulcer
- Pyelonephritis
- Septis (viral, bacterial)
- Severe hemorrhagic shock
- Systemic lupus erythematosus (SLE)
- Thrombotic thrombocytopenic purpura (TTP)
- Viral hepatitis

Patients with HELLP syndrome may present with various signs and symptoms, none of which are diagnostic, and all of which may be found in patients with severe pre-eclampsia-eclampsia without HELLP syndrome. Sibai[6] noted that the patient usually presents remote from term, complaining of epigastric or right upper quadrant pain; some have nausea or vomiting, and others have nonspecific viral syndrome-like symptoms. Most patients (90%) give a history of malaise for the past few days before presentation. In Weinstein's reports,[4,11] nausea or vomiting and epigastric pain were the most common symptoms. Right upper quadrant or epigastric pain is thought to result from obstruction to blood flow in the hepatic sinusoids, which are blocked by intravascular fibrin deposition.

Patients with HELLP syndrome usually demonstrate significant weight gain with generalized edema. It is important to appreciate that severe hypertension (systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥110 mm Hg) is not a constant or even a frequent finding in HELLP syndrome. Although 68.8% of the 112 patients studied by Sibai and associates[16] had a diastolic blood pressure ≥110 mm Hg at the same time of admission to the hospital, 14.5% had a diastolic blood pressure of ≤90 mm Hg. In Weinstein's[4] initial report of 29 patients, less than half[13] had an admission blood pressure ≥160/110 mm Hg. Patients with HELLP syndrome may present with a variety of signs and symptoms

Table 3 Signs and Symptoms in Women with HELLP Syndrome

	Weinstein[11] (n = 57)	Sibai et al.[16] and Audibert et al.[64] (n = 509)	Martin et al.[63] (n = 501)	Rath et al.[65] (n = 50)
RUQ/epigastric pain (%)	86	63	40	90
Nausea/vomiting (%)	84	36	29	52
Headache (%)	NR	33	61	NR
Hypertension (%)	NR	85	82	88
Proteinuria (%)	96	87	86	100

Data are presented as percentage.
HELLP, hemolysis, elevated liver enzymes, and low platelets; NR, not reported; RUQ, right upper quadrant.
Reprinted with permission.[6]

(Table 3) and are often misdiagnosed as having various medical and surgical disorders (Table 2). Sibai[5] therefore recommended that all pregnant women having any of these symptoms should have a complete blood count, platelet count, and liver enzyme determinations irrespective of maternal blood pressure. Imitators of pre-eclampsia, including acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome, and severe sepsis, will be reviewed in a separate article in this series.

Pathology Findings

Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is the hallmark of the HELLP syndrome. Microangiopathic hemolytic anemia is thought to result from the passage of red blood cells through small blood vessels with damaged intima and fibrin deposition,[4,18] leading to the appearance on peripheral smear of triangular cells, burr cells, echinocytes, and spherocytes. Microangiopathic hemolytic anemia is not specific to HELLP syndrome and is also found in association with thrombotic thrombocytopenic purpura, renal disease, hemolytic uremic syndrome, eclampsia, and carcinomatosis.

In a study published by our group,[19] the microscopic findings from liver biopsies obtained under direct visualization after Cesarean delivery from pregnancies complicated by HELLP syndrome were categorized and correlated with the severity of the concurrent clinical and laboratory abnormalities. In comparing the histologic findings with the laboratory findings, periportal hemorrhage correlated with the presence of fibrin deposition but with none of the laboratory parameters measured. Similarly, fibrin deposition was not statistically correlated with any measured laboratory parameter. Although steatosis occurred in only one-third of the patients, it correlated significantly with abnormalities in platelet count, aspartate amino transferase, and total bilirubin but not with periportal hemorrhage or fibrin deposition.

To further test for a relationship between the severity of histologic, clinical, and biochemical parameters in patients with HELLP syndrome, this study group was divided into 2 subgroups by histologic criteria, with 6 patients defined as having mild HELLP syndrome and 5 with severe HELLP syndrome.[19] Statistical analysis demonstrated a significant difference for periportal hemorrhage and fibrin deposition between these 2 histologic criteria groups but failed to show any statistically significant difference in gestational age, mean arterial blood pressure, or any laboratory parameter.

From our study[19] and from previous case reports[20-23] describing the histopathologic findings of hepatic lesions associated with HELLP syndrome, the classic hepatic lesion associated with the HELLP syndrome is periportal or focal parenchymal necrosis in which hyaline deposits of fibrin-like material can be seen in the sinusoids. In addition, immunofluorescence studies show fibrin microthrombi and fibrinogen deposits in the sinusoids in areas of hepatocellular necrosis and in sinusoids of histologically normal parenchyma.[21,23] These histopathologic findings may be related to the elevated liver enzymes and the right upper-quadrant pain and tenderness seen in patients with this syndrome. In certain cases, the cellular necrosis and infarction may be severe enough to be seen by computed tomography (CT) of the liver (Fig. 1).

Initial Management

The clinical course of women with HELLP syndrome is characterized by usually progressive and sometimes sudden deterioration in maternal and fetal conditions. Therefore, patients with suspected diagnosis of HELLP syndrome should be hospitalized immediately and observed in a labor and delivery unit. The first priority is to assess and stabilize maternal condition, particularly coagulation abnormalities (Ta-

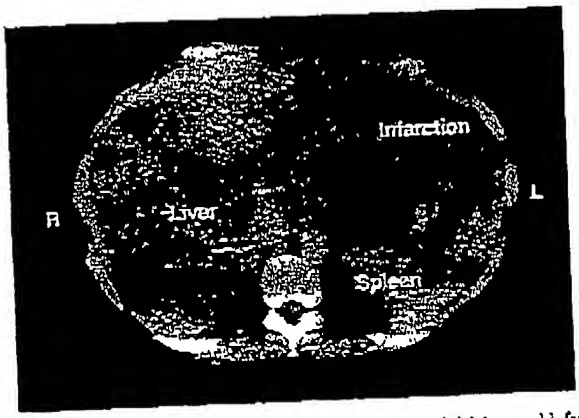

Figure 1 CT axial image through liver and spleen. (L) Maternal left; (R) maternal right. (From Barton JR, Sibai BM. Hepatic imaging in HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count). Am J Obstet Gynaecol 174:1823, 1996; with permission.) (Color version of figure is available online.)

Table 4 Management Outline of Antepartum HELLP Syndrome

I. Assessing and stabilizing the maternal condition
A. Correction of coagulopathy if DIC is present
B. Anti-seizure prophylaxis with magnesium sulfate
C. Treatment of severe hypertension
D. Transfer to tertiary care center, if appropriate
E. Computed tomography or ultrasound of the abdomen if subcapsular hematoma of the liver is suspected
II. Evaluation of fetal well-being
A. Nonstress testing
B. Biophysical profile
C. Ultrasonographic biometry to rule out fetal growth restriction
III. Evaluation of gestational age

ble 4). Patients with HELLP syndrome who are remote from term should be referred to a tertiary care center with appropriate neonatal care facilities.

Patients with HELLP syndrome should be managed as patients with severe pre-eclampsia and initially receive intravenous (IV) magnesium sulfate as prophylaxis against convulsions. In the clinical setting of thrombocytopenia, antihypertensive medications should be administered to keep systolic blood pressure less than 155 mm Hg or diastolic blood pressure less than 100 mm Hg. This effect can be achieved with a 5 mg IV bolus dose of hydralazine, to be repeated as needed every 15-20 minutes for a maximum dose of 20 mg h. Blood pressure is recorded every 15 minutes during therapy and every hour once the desired values are achieved. If hydralazine does not adequately lower blood pressure or if maternal side effects, such as tachycardia or headaches, develop, another drug, such as labetalol or nifedipine, can be used. The recommended dose of labetalol is 20-40 mg IV every 10-15 minutes for a maximum of 220 mg over 1 hour, and the dose of nifedipine is 10-20 mg orally every 30 minutes for a maximum dose of 40 mg over 1 hour. During the observation period, maternal and fetal conditions are assessed.

The recommended regimen of magnesium sulfate is a loading ose of 6 g IV infused over 20 minutes, followed by a maintenance dose of 2 g h^{-1} as a continuous IV infusion. Magnesium sulfate is initiated at the beginning of the observation period, continued during labor and for at least 24 hours postpartum. The next step is to evaluate fetal well-being using the nonstress test of biophysical profile, as well as to obtain ultrasonographic biometry for assessment of possible fetal growth restriction. Finally, it must be decided whether immediate delivery is indicated based on the maternal and fetal status.

A review of the literature highlights the confusion surrounding the management of HELLP syndrome.[5] Some authors consider its presence to be an indication for immediate delivery by Cesarean section, whereas others recommend a more conservative approach to prolong pregnancy in cases of fetal immaturity. Consequently, the literature describes several therapeutic modalities to treat or reverse HELLP syndrome. Most of these therapeutic modalities are similar to those used in the management of severe pre-eclampsia remote from term. Visser and Wallenburg[24] treated 128 pre-eclamptic patients with HELLP syndrome before 34 weeks' gestation with volume expansion and pharmacologic vasodilatation under invasive hemodynamic monitoring in an attempt to prolong pregnancy and thereby enhance fetal maturity. Delivery occurred in 22/128 (17%) of patients within 24 hours; the remaining patients had a median prolongation of pregnancy of 15 days and more than half (55/102) of these women had complete reversal of their laboratory abnormalities. There was no maternal mortality or serious maternal morbidity, but 11 fetal and 7 neonatal deaths occurred. In another series, van Pampus et al.[25] reported the expectant management of 41 women with HELLP syndrome <35 weeks' gestation. Treatment included bed rest, antihypertensive medications, and salt restriction. Delivery occurred within 24 hours in 14/41 (34%). In the remaining 27 patients, the median prolongation of pregnancy was 3 days (range, 0-59 days) and more than half (15/27) had complete normalization of their laboratory abnormalities. There were no serious maternal morbidities; however, there were 10 fetal deaths at 27-35.7 weeks of gestation.

Recently, van Runnard Heimel et al.[26] performed a randomized, double-blind trial in 31 women with HELLP syndrome at <30 weeks' gestation: 15 women received 50 mg prednisolone IV twice a day, and 16 women received a matching placebo. The primary outcome measures were the entry-to-delivery interval and the number of "recurrent HELLP" exacerbations in the antepartum period. The mean entry-to-delivery interval was similar between the 2 groups (6.9 days in prednisolone vs. 8.0 days in the placebo group). There were 3 cases of liver hematoma or rupture, with 1 maternal death in the placebo group. The perinatal mortality rate was 20% in the prednisolone group and 25% in the placebo.

These studies on expectant management of HELLP syndrome show that laboratory abnormalities can reverse in a subgroup of patients. The aim of expectant management, however, is to improve neonatal morbidity and mortality. There is no high-quality evidence demonstrating that overall perinatal outcome in patients with HELLP syndrome is improved with expectant management compared with pregnancies delivered after a course of glucocorticoids. Further, the number of women who were studied in these reports is inadequate to evaluate maternal safety. Therefore, in our opinion, expectant management of HELLP syndrome remains an investigational approach and is contraindicated in women with disseminated intravascular coagulation (DIC).

Corticosteroid Therapy

It is well established that antenatal glucocorticoid therapy reduces neonatal complications and neonatal mortality in women with severe pre-eclampsia at 34 weeks' or less gestation.[27] The recommended regimen of corticosteroids for enhancement of fetal maturity is betamethasone (12 mg intramuscularly every 24 h, 2 doses) or dexamethasone (6 mg intramuscularly every 12 h, 4 doses).[28] These regimens have been identified as the most appropriate for this purpose,

because they readily cross the placenta and have minimal mineralocorticoid activity.

Initial observational studies and small randomized trials suggested use of glucocorticoids may be associated with a more rapid improvement in laboratory and clinical parameters in HELLP syndrome.[10,29,30] These findings, however, have not been supported by subsequent large, randomized, double-blind, placebo-controlled clinical trials. In a trial by Fonseca et al.,[31] 132 women with a gestational age greater than 20 weeks with HELLP syndrome (60 antepartum, 72 postpartum) were randomly assigned to receive either dexamethasone (10 mg IV every 12 hours until delivery and 3 additional doses after delivery) or placebo; postpartum women only received the postpartum doses of dexamethasone or placebo. In their study, dexamethasone did not reduce the duration of hospitalization, the rate of platelet or fresh frozen plasma transfusion, or maternal complications (acute renal failure, pulmonary edema). Although the time of recovery of laboratory tests was not shortened by treatment, subgroup analysis noted that patients with severe HELLP syndrome (platelet count <50,000/mm^3) given dexamethasone had faster platelet count recovery and shorter hospitalization than controls.[31] In a separate double-blind, placebo-controlled trial, Katz et al.[32] randomly assigned 114 postpartum women with HELLP syndrome to receive either IV dexamethasone (10 mg) or IV placebo every 12 hours for 4 days. Use of dexamethasone did not accelerate postpartum recovery of patients with HELLP syndrome. Specifically, there was no difference between drug and placebo groups in the resolution of laboratory or clinical parameters, frequency of maternal complications, need for rescue therapy, or length of hospitalization.[32]

Intrapartum Management

When HELLP syndrome develops at or beyond 34 weeks' gestation, or when there is evidence of fetal lung maturity or fetal or maternal jeopardy before that time, delivery is the definitive therapy. Without laboratory evidence of DIC and absent fetal lung maturity, the patient can be given glucocorticoids to accelerate fetal lung maturity and be delivered 48 hours later. Maternal and fetal conditions should be assessed continuously during this time (Fig. 2).

The presence of HELLP syndrome is not an indication for immediate delivery by Cesarean section. Such an approach may prove detrimental to both mother and fetus. Patients presenting with well-established labor should be allowed to deliver vaginally in the absence of obstetrical contraindications. Otherwise, labor may be initiated with oxytocin infusions as for routine induction in all patients with gestational age over 30 weeks, irrespective of the extent of cervical dilatation or effacement. A similar approach is used for patients at 30 weeks' gestation or less if the cervix is favorable for induction. In patients with an unripe cervix and gestational age under 30 weeks, prostaglandin induction or elective Cesarean sections are options for delivery management.

Maternal analgesia during labor can be provided by intermittent use of small doses (25-50 mg) of intravenous meperidine. Local infiltration anesthesia can be used for all vaginal deliveries. The use of pudendal block is contraindicated in these patients because of the risk of bleeding into this area. Epidural anesthesia should be used with caution as many anesthesiologists are reluctant to place an epidural catheter with a platelet count of less than 75,000/mm^3. General anesthesia is the method of choice for Cesarean sections in the presence of severe thrombocytopenia.

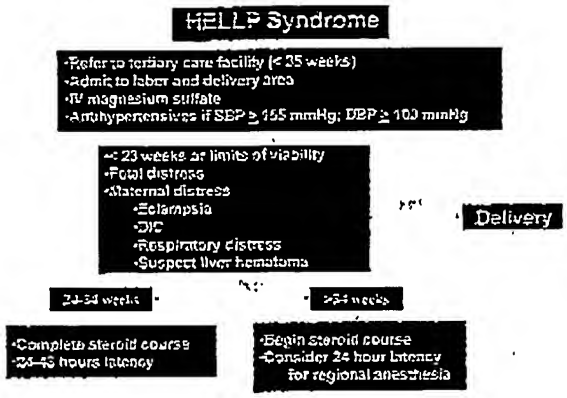

Figure 2 Algorithm for HELLP syndrome management. DBP, diastolic blood pressure; SDP, systolic blood pressure (From Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 103:987, 2004; with permission.) (Color version of figure is available online.)

Platelet transfusions are indicated either before or after delivery in all patients with HELLP syndrome in the presence of significant bleeding (eg, ecchymosis, bleeding from the gums or wound, oozing from puncture sites, intraperitoneal bleeding) and in all those with a platelet count of less than 20,000/mm^3. Correction of thrombocytopenia is particularly important before Cesarean section. Repeated platelet transfusions are not necessary, however, because consumption occurs rapidly and the effect is transient. The authors' policy is to administer 6-10 U of platelets in all patients with a platelet count of less than 40,000/mm^3 before intubating the patient for Cesarean section. Generalized oozing from the operative site is very common, and the risk of hematoma formation at these sites without preventive therapy is approximately 20%. To minimize the risk of hematoma formation, the bladder flap should be left open and a subfacial drain should be used for 24-48 hours.

Hepatic Manifestations

We reported hepatic imaging findings in selected patients with HELLP syndrome and correlated these findings with the severity of concurrent clinical and laboratory abnormalities.[33] Of the 34 patients evaluated in the study, 16 patients (47%) had abnormal hepatic imaging results. The most common CT abnormalities were subcapsular hematoma of the liver (n = 13) and intraparenchymal hemorrhage (n = 6). A magnetic resonance image (MRI) of an unruptured subcap-

Figure 3 T_1-weighted magnetic resonance axial image through liver and spleen. (From Barton JR, Sibai BM. Hepatic imaging in HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count). Am J Obstet Gynaecol 174:1823, 1996; with permission.) (Color version of figure is available online.)

sular hematoma of the liver is depicted in Figure 3. Comparison of the clinical characteristics and laboratory evaluations of patients with normal and abnormal hepatic imaging findings demonstrated a significant difference in platelet count nadir between the patients with normal and abnormal imaging findings but failed to show any statistically significant difference in gestational age, mean arterial pressure, or the other laboratory parameters studied. Of the 13 patients with severe thrombocytopenia (platelet count $\leq 20{,}000/mm^3$), 10 (77%) had abnormal hepatic imaging findings. A separate statistical analysis for patients with and without a subcapsular hematoma of the liver failed to demonstrate any statistical difference for gestational age, mean arterial pressure, or the other laboratory parameters studied. Emergency intervention was needed for 6 patients because of these imaging findings.[33] CT and MRI have excellent sensitivity for detecting acute liver hemorrhage, but because CT was more available, faster, and safer for potentially unstable patients, it was the imaging modality of choice.

Management of Hepatic Complications

Marked elevations in serum aminotransferases are not typical of uncomplicated HELLP syndrome; when they occur, the possibility of hepatic infarction and subcapsular hematoma of the liver must be considered. The differential diagnosis should also include acute fatty liver of pregnancy,[34] abruptio placentae with disseminated intravascular coagulation, ruptured uterus, acute cholecystitis with sepsis, viral hepatitis, and thrombotic thrombocytopenia purpura. Most patients with a subcapsular hematoma of the liver are seen in the late second or third trimester of pregnancy, although cases have been reported in the immediate postpartum period. In addition to the signs and symptoms of pre-eclampsia, physical examination findings consistent with peritoneal irritation and hepatomegaly may be present. Stimulation of the phrenic nerve at the diaphragm can produce referred pain along this nerve's distribution to its origin in the C4-C5 cervical plexus, including the pericardium, peritoneum, pleura, and shoulder. Because the gallbladder and esophagus share innervation by the phrenic nerve with the diaphragm, irritation of the diaphragm may produce sensations of pain in these organs.

Hepatic Infarction

Marked elevation in serum aminotransferases (usually 1000-2000 IU/L or higher) associated with right upper quadrant pain and fever is characteristic of hepatic infarction; this diagnosis can be confirmed by hepatic imaging (Fig. 1). Follow-up imaging after delivery typically demonstrates resolution of the infarcts. These patients may have an underlying procoagulant state, such as the antiphospholipid syndrome.[35,36]

Hepatic Hematoma and Rupture

HELLP syndrome may be complicated by hepatic rupture with the development of a hematoma beneath Glisson's capsule.[33,37,38] Histology of the liver adjacent to the rupture shows periportal hemorrhage and fibrin deposition, along with a neutrophilic infiltrate suggestive of hepatic pre-eclampsia.[37] The hematoma may remain contained, or rupture, with resulting hemorrhage into the peritoneal cavity (Fig. 4). A hepatic hematoma in pregnancy rarely occurs in the apparent absence of pre-eclampsia or HELLP.[39] Women who develop a hepatic hematoma typically have abdominal pain and many have severe thrombocytopenia, shoulder pain, nausea, and vomiting.[33] If hepatic rupture occurs, swelling of the abdomen from hemoperitoneum and shock rapidly ensue. The aminotransferases are usually modestly elevated, but values of 4000-5000 IU/L can occasionally be seen.

The management of a contained hematoma is to support the patient with volume replacement and blood transfusion, as needed, with consideration of percutaneous embolization of the hepatic arteries.[40] If the size of the hematoma remains stable and the laboratory abnormalities are resolving, the patient may be discharged home with outpatient follow-up. It may take months for the hematoma to resolve completely.[33]

Surgical repair has been recommended for hepatic hemorrhage without liver rupture. This complication, however, can be managed conservatively in patients who remain hemody-

Figure 4 Intraoperative photograph of a ruptured subcapsular hematoma of the liver. (Color version of figure is available online.)

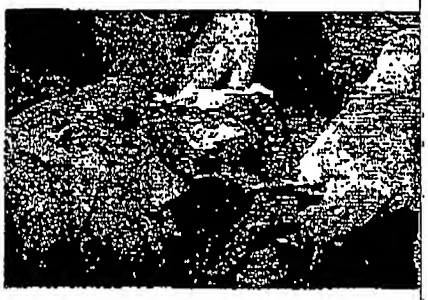

Figure 5 Intraoperative photograph of a laparotomy sponge placed against the liver surface in treatment of a ruptured subcapsular hematoma of the liver. (Color version of figure is available online.)

namically stable.[41,42] Management should include close monitoring of hemodynamics and coagulation status. Serial assessment of the subcapsular hematoma with ultrasound or CT is necessary, with immediate intervention for rupture or worsening of maternal status. It is important with conservative management to avoid exogenous sources of trauma to the liver, such as abdominal palpation, convulsions, or emesis, and to use care in transportation of the patient. Indeed, any sudden increase in intra-abdominal pressure could potentially lead to rupture of the subcapsular hematoma.[43]

Rupture of a subcapsular hematoma of the liver is a life-threatening complication of HELLP syndrome. In most instances, rupture involves the right lobe and is preceded by the development of a parenchymal hematoma. Patients frequently present with shoulder pain, shock, or evidence of massive ascites, respiratory difficulty, or pleural effusions, and often with a dead fetus. An ultrasound or computed axial tomography of the liver should be performed to rule out the presence of subcapsular hematoma of the liver and assess for the presence of intraperitoneal bleeding.

The presence of ruptured subcapsular liver hematoma resulting in shock is a surgical emergency requiring acute multidisciplinary treatment. Resuscitation should consist of massive transfusions of blood, correction of coagulopathy with fresh frozen plasma and platelets, and immediate laparotomy. A team experienced in liver trauma surgery should be consulted[44] if hepatic rupture is suspected; an incision in the upper abdomen is necessary for adequate surgical exposure. A lower abdominal midline incision can be extended superiorly. If a Pfannenstiel's incision was used for operative delivery, then a separate upper abdominal incision should be made to maximize visualization of the upper abdomen and liver. Options at laparotomy include packing (Fig. 5) and drainage, surgical ligation of the hemorrhaging hepatic segments, embolization of the hepatic artery to the involved liver segment, and loosely suturing omentum or surgical mesh to the liver to improve integrity. Shrivastova et al.[45] in a recent case report described the successful use of an argon beam coagulator to obtain hemostasis from a ruptured liver hematoma in a patient with HELLP syndrome, although our previous experience with this modality was unsuccessful (JR Barton and BM Sibai, unpublished data). Even with appropriate treatment, maternal and fetal mortality is over 50%. Mortality is most commonly associated with exsanguination and coagulopathy. Initial survivors are at increased risk for developing adult respiratory distress syndrome, pulmonary edema,[46] and acute renal failure in the postoperative period.[47,48] Smith et al.[49] reviewed their management of 7 patients with spontaneous rupture of the liver occurring during pregnancy. Of the 4 survivors, the mean gestational age was 32.8 weeks and the mean duration of hospitalization was 16 days. All the survivors were managed with packing and drainage of the liver, whereas the 3 patients treated with hepatic lobectomy died. The authors also extracted 28 cases from the literature reported since 1976. From 35 cases analyzed, there was an 82% overall survival for the 27 cases managed by packing and drainage, whereas only 25% of 8 patients undergoing hepatic lobectomy survived. The authors emphasized that hepatic hemorrhage with persistent hypotension unresponsive to transfusion of blood products may be managed surgically with laparotomy, evacuation of the hematoma, packing of the damaged liver, and draining of the operative site.[49] In certain cases where the patient is stable enough to undergo angiography, transcatheter embolotherapy is a reasonable alternative to surgery.[50]

More recently, Reck et al.[51] reviewed 53 cases with HELLP syndrome-associated liver rupture (4 patients from their center in Germany and 49 identified from a MEDLINE literature search covering 1990-1999). Despite surgical interventions, HELLP syndrome-associated liver rupture carried a mortality of 39% (19/49) in their review. The main causes of death were hemorrhagic shock (n = 11) or multiorgan failure (n = 7).[51] Based on their review, the authors suggested an interdisciplinary approach for patients with ruptured liver or hepatic failure, including the use of temporary packing of the liver to control bleeding. In those patients with hepatic failure or uncontrollable hepatic hemorrhage, they noted a liver transplant as a last resort measure must be considered.[51]

Liver Transplantation for Intractable Hemorrhage

For patients with intractable hemorrhage despite the above described interventions or those with necrosis with subsequent liver failure, liver transplantation[52-54] has been successful in case reports and case series. Shames et al.[52] queried the Organ Procurement and Transplantation Network database regarding liver transplants performed for complications from HELLP syndrome. Eight deceased donor liver transplants were identified in the USA with this indication between October 1987 and November 2003. At the time of their review, 6 of the 8 patients were alive with both deaths occurring within 1 month of transplantation. Two patients had required retransplantation. Based on the results in their review, these authors presented an algorithm where liver transplantation is considered for patients with complicated HELLP syndrome, including ongoing, uncontrolled hemorrhage or liver necrosis and failure.[52]

Zarrinpar et al.[53] described 8 women without a history of liver disease who underwent liver transplantation at their institution (UCLA) between February 1984 and December 2006 for complications of HELLP syndrome. All received cadaveric grafts with a mean interval from delivery to liver transplantation of 7 days. There were no intraoperative

Table 5 Management of Patients with Documented Subcapsular Hematoma of the Liver

General considerations:
- I. Have the blood bank aware of the potential need for large amounts of packed red blood cells, fresh frozen plasma, and platelet concentrate
- II. Consultation of a general or vascular surgeon
- III. Avoid direct and indirect manipulation of the liver
- IV. Close monitoring of hemodynamic status
- V. Intravenous magnesium sulfate to prevent seizures

If the hematoma is unruptured:
- I. Conservative management
  - A. Correct coagulopathy
  - B. Serial computed tomography scans or ultrasound

If the hematoma is expanding or ruptured:
- I. Massive transfusions
- II. Immediate laparotomy
  - A. If bleeding is minimal:
    1. Observation
    2. Draining area with closed suction
  - B. If bleeding is severe:
    1. Application of laparotomy sponges as packs for pressure
    2. Embolization of the hepatic artery to the involved liver segment
    3. Surgical ligation of haemorrhaging hepatic segment
    4. Loosely suture omentum or surgical mesh to the liver to improve integrity
    5. Argon beam coagulator to liver surface
    6. Hepatic lobectomy
    7. Hepatectomy and temporary portal caval shunt followed by liver transplant

deaths. There was 1 death from sepsis on postoperative day 19 and 1 death from cholangitis/sepsis more than 5 years postoperatively. After liver transplantation, they reported the Kaplan-Meier patient survival at 1, 5, and 10 years were 88%, 88%, and 65%, respectively; 1-, 5-, and 10-year graft survival rates were 64%, 64%, and 48%, respectively.[53] Marsh et al.[55] in their review on surviving hepatic rupture in pregnancy make an important observation concerning liver transplantation. They note that due to the very small number of available organs, death before transplantation is a concern. They suggest potential candidates are only those in whom all other measures fail to control hemorrhage, or when the liver has become devascularized such that there is no other alternative.[55]

From our experience and review of the literature, we have developed an algorithm for the management of hepatic complications of HELLP syndrome (Table 5). This algorithm emphasizes the potential for transfusion of large amounts of blood and blood products and the need for aggressive intervention if rupture of the hematoma is suspected. We recommend 30 U of packed red blood cells, 20 U of fresh frozen plasma, 30-50 U of platelets, and 20-30 U of cryoprecipitate be available if rupture of a subcapsular hematoma is suspected. Our experience agrees with the observations of Smith et al.[49] in that a stable patient with an unruptured subcapsular hematoma should be conservatively managed. Constant monitoring must continue during this management, however, because patients can rapidly become unstable after rupture of the hematoma. Survival clearly is associated with rapid diagnosis and immediate medical or surgical stabilization. Coagulopathy must be aggressively managed because failure to do so is associated with an increased incidence of renal failure. In addition, these patients should be managed in an intensive care unit facility with close monitoring of hemodynamic parameters and fluid status to avoid the potential for pulmonary edema or respiratory compromise.

Postpartum follow-up for patients with subcapsular hematoma of the liver should include serial CT, MRI, or ultrasonography until the defect resolves. For patients receiving numerous transfusions, the hepatitis and human immunodeficiency virus status as well as iso-antibody development should be assessed. Although the data on subsequent pregnancy outcome after a subcapsular hematoma of the liver in pregnancy are limited, we have managed 3 such patients who have had subsequent normal maternal and fetal outcomes and Wust et al.[56] reported the successful outcome of 4 subsequent pregnancies in 3 women with a history of hepatic rupture and pre-eclampsia/HELLP syndrome.

Postpartum Management

The HELLP syndrome may develop antepartum or postpartum. An analysis of 442 cases by Sibai et al.[37] revealed that 309 (70%) cases had evidence of the syndrome antepartum, and 133 (30%) developed the manifestations postpartum. In the postpartum period, the time of onset of the manifestations ranged from a few hours to 7 days with most developing within 48 hours postpartum. Patients in this group are at an increased risk for the development of pulmonary edema with acute renal failure.[47,57] Management is similar to that of the antepartum patient with HELLP syndrome, including the need for anti-seizure prophylaxis. Hypertension control may be more aggressive, however, because there is no longer concern about compromising the uteroplacental circulation in the postpartum patient.

Following delivery, the patient should be monitored closely in an intensive care setting for at least 48 hours. Laboratory values may initially worsen after delivery. The time course of recovery from HELLP syndrome was evaluated in a series of 158 women with the disease by Martin et al.[58] Decreasing platelet counts continued until 24-48 hours after delivery, while serum LDH concentration usually peaked 24-48 hours postpartum. In all patients who recovered, a platelet count greater than 100,000/mm^3 was achieved spontaneously by the sixth postpartum day or within 72 hours of the platelet nadir. An upward trend in platelet count and a downward trend in LDH concentration should be seen by the fourth postpartum day in the absence of complications. More recently, Hupuczi et al.[59] reported similar findings. Recovery can be delayed in women with particularly severe disease, such as those with DIC, platelet count <20,000/mm^3, renal dysfunction, or ascites.

Recurrence in Subsequent Pregnancies

Data defining the recurrence risk of HELLP syndrome are sparse. In 3 series, including almost 400 pregnancies in women with a history of HELLP syndrome, the rate of recurrence was only 2%-6%.[60-62] By comparison, women with a history of HELLP syndrome are at high risk for developing pre-eclampsia in a subsequent pregnancy. In a series by Sibai et al.[60] that included 152 such women with 212 subsequent pregnancies, the incidence of pre-eclampsia varied from 19% in normotensive women to 75% in those with underlying hypertension. Another report[62] was limited to 48 women with second-trimester HELLP syndrome who had 62 subsequent pregnancies that progressed beyond 20 weeks of gestation. Pre-eclampsia occurred in 27 of 52 (52%) subsequent pregnancies in normotensive women and 7 of 10 (70%) pregnancies in women with chronic hypertension.

Pancreatic Involvement of Pre-Eclampsia

Acute pancreatitis is a rare complication of pregnancy. Eddy et al.[66] identified 101 cases of pancreatitis in pregnancy during a 10-year period from 15 tertiary care and community hospitals in urban and suburban settings in 3 midwestern states. Their reported incidence of acute pancreatitis in pregnancy was 1 in 3428, similar to the incidence of 1 in 1333 observed by Ramin et al.[67] from the University of Texas Southwestern Medical Center in Dallas. Most cases (66%) of acute pancreatitis in the study by Eddy et al.[66] were biliary in origin and associated with better outcomes than nonbiliary causes.

Acute pancreatitis is characterized by epigastric tenderness, pain, nausea, and vomiting as well as abdominal distension. Laboratory findings include elevated levels of pancreatic enzymes (amylase, lipase, trypsin), leukocytosis, and electrolyte abnormalities, including decreased serum calcium and increased potassium. Medical therapy is the preferred management of acute pancreatitis in pregnancy, including bowel rest, intravenous hydration, correction of metabolic abnormalities, and pain control.

As pre-eclampsia has been associated with vascular endothelial injury in placental,[1] hepatic, and cerebral vessels, it is reasonable to assume that similar injury could occur in the pancreas. Acute pancreatitis has been reported in association with HELLP syndrome[68] and pre-eclampsia.[69,70] Hojo et al.[68] reviewed 15 cases in the literature of pre-eclampsia-associated acute pancreatitis, all without cholelithiasis, as well as a single case managed at their institution in Japan. They noted the onset of pancreatitis during pregnancy in 6 cases and the postpartum period in 10 cases. This presentation differed significantly from acute pancreatitis in pregnancy not associated with pre-eclampsia where most cases (97%) occurred in the antepartum period.[67] The authors[68] concluded that ischemia with pre-eclampsia cannot only damage the liver, but also the pancreas and gallbladder. Certainly, if pancreatic involvement were coexistent with HELLP syndrome, we would recommend management with delivery.

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EXHIBIT B

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Proteinuria as a predictor of complications of pre-eclampsia

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Proteinuria as a predictor of complications of pre-eclampsia

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Abstract

Proteinuria is a defining criterion for the diagnosis of pre-eclampsia. The amount of protein lost per day has been thought by some to predict both maternal and fetal outcome. The systematic review of 16 primary papers including over 6700 patients by Thangaratinam and colleagues published this month in BMC Medicine suggests otherwise. This finding may influence our management of pre-eclampsia.

Commentary

Proteinuria has been proposed and studied as both an indicator of severity of disease and as a predictor of outcome in pre-eclampsia. Many clinicians still make major management decisions based on the degree of proteinuria in such patients. The systematic review by Thangaratinam and colleagues [1] published this month in BMC Medicine suggests however that proteinuria is a poor predictor of either maternal or fetal complications in women with pre-eclampsia, and provides information that may have significant clinical implications.

Pre-eclampsia affects 2 to 3% of all pregnancies and is responsible for about 60,000 maternal deaths every year, mainly in poor countries [2]. Annually only 10 of these deaths occur in the UK [3], approximately 40 to 50 in the USA [4], while in comparison more than 200 occur in South Africa [5]. The only known cure for pre-eclampsia is delivery of the placenta. This creates a conflict of interest between the individuals on either side of the placenta: the mother stands to benefit from early delivery, while the baby may suffer complications of prematurity if born too early. Conservative management of pre-eclampsia to gain time for the baby to mature inevitably places the mother at risk [6]. Pre-eclampsia is usually a progressive disease, but the rate of progression and the occurrence of catastrophic complications such as eclampsia, cerebrovascular accident, severe HELLP syndrome, pulmonary

edema or renal failure are difficult to predict. Any marker which could reliably predict the likelihood of serious complications would be very valuable for helping choose the optimal time for delivery.

Proteinuria is a defining dysfunction of pre-eclampsia [7]. Quantitation of a timed collection has been the gold standard for many decades and is expressed as the amount of protein excreted in the urine per unit time. Twenty-four-hour specimens have been traditionally used, but more recently 12-hour collections (and even 2-hour collections) have been validated [8]. The urinary protein:creatinine ratio is used in some institutions instead of a timed protein collection [9], with some finding it to be equally useful in determining pathologic proteinuria with the advantage of not requiring a timed collection, while others have not been as confident [10]. A 24-hour collection remains the standard of care in the USA [7].

The severity of the proteinuria in pre-eclampsia has been regarded by some as a predictor of adverse outcomes for the mother [11]. Others have been less sanguine about the relationship [12]. A reliable correlation between the level of proteinuria and severity of pre-eclamptic complications would be extremely valuable for clinical decision making.

The review by Thangaratinam et al [1] reported in this issue sets a new standard for systematically searching for, evaluating and aggregating the results of studies of this kind. The results are disappointing in that the correlation found between level of proteinuria and severity of clinical disease was insufficiently reliable to be clinically useful. The authors reported that from a fetal point of view, the only statistically significant findings were that proteinuria of 5g/24h in a timed specimen, or 1+ and 3+ in a dipstick specimen, predicted stillbirth with a likelihood ratio for the positive result of 1.3 to 2.3 ('little useful' to 'somewhat useful'). Maternal outcomes fared equally poorly. The same group of authors has previously reported on another biochemical marker, serum urate, with similarly disappointing results [13].

Despite the rigor and efforts to determine the quality of the studies included in the current review, practice differences, equipment changes, and definitions of pre-eclampsia could have influenced the diagnosis (and management) of pre-eclampsia over the time period of the studies used. Thirty years ago changes in systolic pressure and diastolic pressure during gestation were being used to define pre-eclampsia (the so-called 30/15 rule) and if the diagnosis of pre-eclampsia is differently defined in different studies the validity of the result may be diminished.

A very important potential confounding factor to consider in studies of the kind reviewed, is that the test result (in this case severe proteinuria), particularly in the earlier studies, may have dictated management. In the USA at least, proteinuria of 5g or more per 24 hours is one of the diagnostic criteria for severe pre-eclampsia [7]. If women were delivered earlier as a result of a positive test for severe proteinuria then that test cannot be stated to have been used to predict outcome, since its result was used to intervene and thus influence the outcome. Earlier delivery precipitated by a positive test result may, for example, reduce maternal complications (leading to an underestimation of the predictive value of the test), or increase perinatal morbidity due to prematurity, leading to an overestimation. The test would technically have an association with the outcome, rather than a predictive capability.

Despite these limitations, this metanalysis appears to confirm what clinicians have suspected for a long time. The degree of proteinuria alone does not have a strong association with adverse outcome. Maternal and fetal clinical condition and gestational age, complemented by hematologic and biochemical parameters, should for the time being remain the primary determinants for timing delivery in women with pre-eclampsia.

As the results of observational studies may systematically over- or underestimate the predictive value of tests as discussed above, a randomized trial of knowledge versus no knowledge of the level of proteinuria to guide management would be justified.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MAB and GJH drafted the manuscript and MAB revised it for important intellectual content. MAB and GJH have both given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for the content.

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